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Commentary

Euglycemic diabetic ketoacidosis: a potential pitfall for the emergency physician

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes mellitus that can occur in patients with type 1 or type 2 diabetes. The triad of hyperglycemia, metabolic acidosis with an increased anion gap, and ketosis heralds the familiar clinical presentation of DKA. The mechanisms involved in this metabolic disturbance are due to absolute or relative insulin deficiency. Euglycemic DKA (eu-DKA) was first described in 1973 and is characterized by ketoacidosis and electrolyte derangement with only marginal or absent elevation of serum glucose, often < 11.0 mmol/L (200 mg/dL) [1].

Although an uncommon diagnosis, the absence of hyperglycemia in eu-DKA poses a potential pitfall for the unsuspecting emergency physician, often leading to delays in diagnosis and commencement of treatment, carrying with it the potential for adverse metabolic consequences and increased mortality.

The aim of this article is to review the clinical presentation of eu-DKA and its pathophysiology and treatment.

CLINICAL PRESENTATION OF EUGLYCEMIC DIABETIC KETOACIDOSIS

Patients with eu-DKA typically present with symptoms such as malaise, dyspnea, nausea, vomiting, and abdominal pain, similar to patients with conventional DKA [2]. The most important step in diagnosis of eu-DKA is considering it as an option and not being falsely reassured by the presence of normoglycemia. Any patient with diabetes demonstrating these symptoms should be screened for eu-DKA with blood pH and blood or urine ketone testing, although eu-DKA may be the first presentation of diabetes.

A patient with eu-DKA will typically have normoglycemia in the presence of metabolic acidosis (pH less than 7.3) and decreased blood bicarbonate (less than 18 mmol/L) [2]. Serum and urine ketones must be elevated to qualify as eu-DKA [2].

Lactic acid may be elevated but should not be the sole reason for the increased anion gap. High lactate level in the absence of ketosis suggests that an alternative diagnosis should be sought.

Leukocytosis may be present with concurrent infection; however, it may result from hemoconcentration due to dehydration or a stress response associated with acute illness [2]. Other markers of infection should be sought before attributing it as the precipitating factor.

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Total potassium level is often depleted in eu-DKA, but blood potassium may be normal. Mild hyponatremia may also be seen but is typically less marked than the "pseudohyponatremia" seen in profound hyperglycemic states [2].

EPIDEMIOLOGY

With reported incidences ranging from 2.6% to 3.2% of patients admitted with DKA [3], eu-DKA is a relatively uncommon diagnosis, with no demonstrable difference between sexes.

MECHANISMS OF EUGLYCEMIC DIABETIC KETOACIDOSIS

It is believed that eu-DKA primarily occurs due to a carbohydrate deficit, which leads to increased lipolytic activity and subsequent ketoacidosis [2]. The causes of eu-DKA can be divided into two main groups: glucose wasting (due to such events as glucosuria or persistent vomiting) and low level of hepatic glycogen (due to such events as starvation and chronic alcoholism).

Typically, serum insulin level is low in eu-DKA patients, with an associated excess of counterregulatory hormones such as glucagon, cortisol, and adrenaline [2]. Significant volume depletion occurs due to osmotic diuresis from glucosuria, often further exacerbated by reduced oral intake and vomiting.

Alcoholic ketoacidosis

Alcoholic ketoacidosis should be considered a subclass of eu-DKA and carries a significant risk of mortality in patients with alcohol dependence [2]. Chronic alcohol consumption causes insulin resistance and destroys pancreatic beta cells [4]. These factors, combined with the effects of poor dietary intake, reduce the body's storage of glycogen in the liver and the glucose reserve. Consequently, even short periods of fasting in individuals with chronic alcoholism can result in life-threatening ketoacidosis.

Euglycemic diabetic ketoacidosis in pregnancy

Maternal hormones, such as human placental lactogen and increased level of cortisol, contribute to increased insulin resistance in the pregnant patient [5]. Even overnight fasting can lead to increased fat breakdown and ketogenesis and is further compounded by the respiratory alkalosis that occurs during pregnancy. This decreases blood bicarbonate, reducing the body's ability to buffer organic acids. These factors combine to increase the likelihood of ketoacidosis during pregnancy.

Consequently, short periods of starvation during pregnancy, such as those experienced during episodes of vomiting, decreased appetite, or intercurrent illness, lead to glucose depletion and ketogenesis, which may proceed to eu-DKA. Most documented cases of eu-DKA during pregnancy occurred in patients with type 1 diabetes [6]. However, there is a growing body of evidence reporting eu-DKA in patients with type 2 diabetes [7] and in nondiabetic pregnant women with intercurrent illnesses [8,9].

SGLT2 inhibitors

The year 2011 saw the introduction of sodium glucose transporter 2 (SGLT2) inhibitors, a class of drugs that includes dapagliflozin and canagliflozin, used in the management of patients with type 2 diabetes. Transport proteins in the proximal tubule of the kidney reabsorb glucose and sodium from urine independent of insulin. SGLT2 inhibitors block this mechanism, leading to glucosuria and natriuresis. Several benefits of SGLT2 inhibitors have been identified in therapeutic treatment of patients with diabetes, including better blood pressure management and improved glucose control. These drugs may also provide a cardiorenal protective role. However, since their launch, there have been several published case reports describing eu-DKA in patients treated with this class of drugs [10–12]. Initially used exclusively in the management of type 2 diabetes mellitus, the intended population for this group of drugs was expanded to include select patients with type 1 diabetes. However, due to the high incidence of DKA in this group [13], authorization for use in type 1 patients was withdrawn in the United Kingdom in December 2021 [14]. The US Food and Drug Administration (FDA) and the European Medicines Agency also issued warnings in 2015 and 2016, respectively, on predisposing factors to development of eu-DKA in patients with type 2 diabetes mellitus taking SGLT2 inhibitors [15].

The incidence of eu-DKA in patients with type 2 diabetes taking SGLT2 inhibitors is reported to be approximately 0.1% [16]. Data published by the FDA in 2021 reported the median time to ketoacidosis after initiation of SGLT2 inhibitor therapy was 43 days [15]. In a different case study, 50% of patients who developed eu-DKA while taking SGLT2 inhibitors had clear precipitating events, such as acute illness (e.g., infection and surgery), reduced oral intake, and reduced insulin dose [17]. Fralick et al. [18] reported that type 2 diabetes patients taking SGLT2 inhibitors are more than twice as likely to develop diabetic ketoacidosis within 180 days of follow-up compared with patients receiving other oral hypoglycemic agents.

TREATMENT

Early involvement of a multidisciplinary team including an experienced endocrinologist in the management of this patient group

is paramount. The initial patient management is directed toward fluid resuscitation, as patients usually present with profound dehydration. Fluid resuscitation using intravenous crystalloid should continue until the anion gap and the acidosis have resolved [2].

In contrast to conventional DKA management, 5% dextrose should be added to the fluid resuscitation regime to avoid hypoglycemia and hasten the clearance of ketosis. An increase to 10% dextrose should be considered if ketoacidosis persists on 5% dextrose [3].

Given that patients in eu-DKA have blood glucose level less than 11.0 mmol/L (200 mg/dL), Modi et al. [19] suggest commencing insulin infusion at a rate of at least 0.02 to 0.05 units/kg/hr. Decreasing the rate further may result in insufficient insulin in patients with type 1 diabetes and may not aid in resolution of ketoacidosis. Other authors suggest starting the insulin infusion at a slightly higher rate [2]. Blood glucose level should be assessed hourly at first and electrolytes monitored every 4 hours as intravenous supplementation of potassium and other electrolytes may be required [2].

Patients taking SGLT2 inhibitors should discontinue these medications as soon as the diagnosis is recognized and should not be restarted until the patient has fully recovered from the acute illness [12]. Sodium bicarbonate infusions are not indicated, and their use in the setting of severe acidemia (pH less than 6.9) is controversial [2].

CONCLUSION

For an unsuspecting emergency physician, eu-DKA is a diagnostic challenge, primarily due to the absence of hyperglycemia. Understanding the various mechanisms that lead to eu-DKA and the various contexts in which it can occur, particularly the at-risk groups, will increase consideration of eu-DKA as a potential diagnosis. Treatment focuses on aggressive hydration, glucose replacement, insulin administration, and correction of any electrolyte imbalance, as well as treating the precipitating cause.

Morbidity and mortality can be significantly improved by early diagnosis and initiation of treatment [2]. Intercurrent illness, prolonged vomiting, chronic alcoholism, and SLGT2 inhibitors must be considered as potential triggers for eu-DKA in patients presenting with acidosis and an increased euglycemic anion gap, remembering that pregnant women and the malnourished are especially at risk.

Introduction of SGLT2 inhibitors has highlighted the diagnosis of eu-DKA. Due to the favorable cardiorenal protective effects of these drugs, their use is expected to increase significantly among patients with type 2 diabetes. To support this, appropriate education of both the patients and physicians, including those in the emergency department, should take place to ensure eu-DKA is considered as a diagnosis and timely treatment is commenced in patients taking this class of drugs.

CONFLICT OF INTEREST

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